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Comparison of metastatic versus non-metastatic breast cancer at the time of diagnosis and risk factors for primary metastatic breast cancer

Mesut Yur

Firat University, Faculty of Medicine, Department of Surgical Oncology, Elazig, Türkiye

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Abstract

Aim: The most common type of cancer in women is breast cancer. Despite an increase in the rate of early detection, distant organ metastasis is still seen at the time of diagnosis. The purpose of this study was to identify the predictive risk factors for breast cancer patients with distant organ metastases and to compare them to those without distant organ metastases.

Materials and Methods: The study included data from patients who applied to our clinic for follow-up or treatment between January 2020 and July 2020. After meeting the exclusion criteria, the remaining 115 patients were included in the study. Study participants were divided into two groups: metastatic (group I) and non-metastatic (group II). Logistic regression analysis is used to assess the predictive risk factors.

Results: There is a significant difference between groups in terms of the breast side, T-stage, N-stage, CA 15-3, and albumin levels ($p< 0.05$). In univariate analyses, T-stage, CA 15-3, estimates glomerular filtration rate (eGFR), alkaline phosphatase, and albumin levels were statistically found to be significant ($p<0.05$). In multivariate analysis, CA 15-3 (OR: 1.017; 95% CI: 1.005-1.030, $p = 0.006$), eGFR (OR: 0.944; 95% CI: 0.894-0.996, $p = 0.034$), and albumin (OR: 0.087; 95% CI: 0.011-0.676, $p = 0.020$) were found to be predictive risk factors for metastatic breast cancer.

Conclusion: High T-stage, N positivity, high CA15-3 levels, and low albumin levels were observed in the metastatic breast cancer group. CA 15-3, eGFR, and albumin levels were found to be predictive factors for metastatic breast cancer at the initial diagnosis. New studies are needed to validate these findings.

Introduction

Breast cancer is the most frequent cancer in women. It is the second-leading cancer-related cause of death worldwide [1]. Breast cancer detection in its early stages has increased as a result of breast cancer screening [2]. For the diagnosis of breast cancer, numerous biomarkers have been studied [3, 4]. However, their use has not been demonstrated in clinical practice. CA 15-3 and CEA are the two most frequently utilized tumor markers in breast cancer. But they cannot be used to diagnose breast cancer [5]. These tumor markers are primarily used in postoperative follow-up to detect early recurrences and distant metastases [6-8].

Despite improvements in early detection, metastatic breast cancer is still seen at the time of diagnosis [9, 10]. Breast cancer is a systemic disease, and if distant metastases are detected, the treatment for the disease needs to be altered [5]. So, screening tests like computed tomography, positron emission tomography-computed tomography (PET-CT), magnetic resonance imaging, and bone scintigraphy are used to look at the bones, liver, and lungs, which are the most common places for breast cancer to spread [5].

There is no study examining the characteristics of breast cancer patients with distant organ metastasis in the literature. This study primarily aims to investigate the predictive risk factors associated with distant organ metastasis in breast cancer patients. The second aim is to compare the breast cancer patients with distant organ metastasis to non-metastatics.

Materials and Methods

After acquiring approval from the ethics committee (Non-invasive Research Ethics Committee of Fırat University;

*Corresponding author:
Email address: myur@firat.edu.tr (Mesut Yur)

approval number: 2023/10-24) and the institution, the study was initiated. Data from female patients who applied for follow-up or treatment suffering for breast cancer between January 2020 and July 2020 were scanned electronically. The study involved all patients who were evaluated by a multidisciplinary oncology council (medical oncology, radiology, and surgical oncology) and for whom the council decided to initiate treatment.

Exclusion criteria

Other system cancers, systemic immune disease, systemic immune treatment, benign ovarian cysts, benign breast disease, benign/chronic liver disease, sarcoidosis, and lupus are excluded. Blood samples collected after surgery or neoadjuvant therapies were not considered. The absence of standard metastasis screenings (chest and abdominal tomography) or PET-CT screenings was ruled out. Patients with missing data or metastases within three months of the initial diagnosis were excluded. Study participants were divided into two groups: metastatic breast cancer patients (group I) and non-metastatic (group II) at the time of their initial diagnosis.

Laboratory data

CA 15-3 levels, CEA levels, glucose levels, estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP) levels, albumin levels, calcium levels, neutrophyl-to-lymphocyte ratio levels (NLR), and systemic immune inflammation index (SII) were obtained from all patients' data. SII and NLR were calculated as neutrophil*platelet/lymphocyte and neutrophil/lymphocyte, respectively.

Pathology records

All pathological data were analyzed for tumor histological type, tumor diameter, T-stage, axillary lymph node metastasis status (N(0) or N(+)), hormone receptor status, grades, and lymphovascular invasion. The receptor status of patients who had received neoadjuvant treatment was examined in the Trucut biopsy records.

Hormone receptor status considering

Estrogen receptor status was assessed via the Olympus microscope digital camera model DP71 (Olympus Co.; Shinjuku, Tokyo, Japan) software imaging system. A positive PR status was defined as 10% or more positively stained nuclei. HER2 status positivity; 3+ of IHC staining (uniform, intense membrane staining of 30% of invasive tumor cells) were considered positive, and if the HER-2/neu gene was amplified using fluorescence in situ hybridization, 2+ staining was too. Negative characteristics included a HER2 status of 1+ and the absence of staining.

Categorizing luminal types

Luminal type A was considered estrogen receptor (ER) and/or progesterone receptor (PR) positive, HER2 negative, and Ki-67 $<$ %14. Luminal type B Her2 (-) was considered ER and/or PR positive, HER2 negative, and Ki-67 $\geq$ %14. Luminal type B Her2(+) was considered ER and/or PR positive, and HER2 positive. HER2 like was considered ER and PR negative, and HER2 positive. Triple-negative was considered ER, PR, and HER2 negative.

Statistical analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the normality of the distribution of the data. Nonparametric data are typically represented by the median value, accompanied by the range of values (minimum to maximum). In contrast, parametric data are commonly expressed as the mean value along with the standard deviation (SD). Comparing parametric and nonparametric data was done using the independent samples t-test and Mann-Whitney U test, respectively. Categorical data were analyzed using the chi-square or Fisher's exact test. A logistic regression analysis (Forward LR method) was conducted to identify significant predictors of metastatic breast cancer. Hosmer and Lemeshow test was used to test the validity of the model. Significant variables from the univariate analysis were entered into multiple logistic regression analyses. The results were presented as odds ratios (OR) with related 95% confidence intervals (CI). For all tests, the statistical level of significance was set at $p<0.05$.

Results

Demographic data on patients

The study comprised a total of 115 female patients. The mean age of the patients was 54.14 ± 12.82 years. Distant organ metastasis (Group I) was present in 16 (13.9%) patients, and axillary lymph node metastases were present in 78 (67.8%) patients. There were 13 (11.3%) patients with bone metastases, 10 (8.7%) with lung metastases, 4 (3.5%) with liver metastases, 3 (2.6%) with brain metastases, and 1 patient with peritoneal metastases (Table 1). The median value for CA 15-3 was 17.6 (3.3–1841) U/mL, and the median value for CEA was 1.58 (0.01–138) ng/mL. Other data are shown in Table 1.

Comparison of groups

When the groups were compared with each other, statistically significant differences were found in terms of the breast side, T-stage, N-stage, CA 15-3, and albumin levels ($p<0.05$) (Figure 1). In group I, higher T-stage and N-stage positivity, high CA 15-3 levels, and low albumin levels were observed. No significant differences were observed

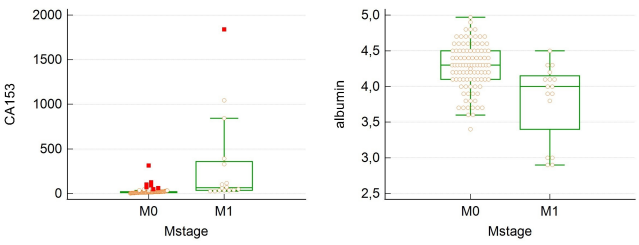

Figure 1. Boxplot graphic of CA 15-3 and albumin levels in metastatic (M1) and nonmetastatic (M0) patients.

Table 1. Demographic and laboratory data of the patients.

Variables		n=115 (100%)
Age /years)		54.14 ± 12.82
Menopausal status	Premenopausal	51 (44.3%)
	Postmenopausal	64 (55.7%)
Breast side	Left	57 (49.6%)
	Right	55 (47.8%)
	Bilateral	3 (2.6%)
Tumor type	IDC	107 (93%)
	ILC	6 (5.2%)
	Mixt type	2 (1.7%)
T-stage	1	41 (35.7%)
	2	58 (50.4%)
	3	11 (9.6%)
	4	5 (4.3%)
N-stage	N (0)	37 (32.2%)
	N (+)	78 (67.8%)
M-stage	M 0	99 (86.1%)
	M 1	16 (13.9%)
ER	Positive	86 (74.8%)
	Negative	29 (25.2%)
PR	Positive	71 (61.7 %)
	Negative	44 (38.3%)
HER2	Positive	39 (33.9%)
	Negative	76 (66.1%)
Luminal types	Luminal A	20 (17.4%)
	Luminal B HER2 negative	40 (34.8%)
	Luminal B HER2 positive	30 (26.1%)
	HER2 like	9 (7.8%)
	Triple-negative	16 (13.9%)
Bone metastasis	Positive	13 (11.3 %)
	Negative	102 (88.7%)
Lung metastasis	Positive	10 (8.7%9)
	Negative	105 (91.3%)
Liver metastasis	Positive	4 (3.5%)
	Negative	111 (96.5%)
Brain metastasis	Positive	3 (2.6%)
	Negative	112 (97.4%)
Other metastasis	Positive	1 (0.9%)
	Negative	114 (99.1%)
Tumor diameter (mm)		25 (4-110)
CA 15-3 (U/mL)		17.6 (3.3-1841)
CEA (ng/mL)		1.58 (0.01-138)
eGFR (mL/sc/1.73m^2)		90 (25.31-90)
Glucose (mg/dL)		101 (71-312)
ALP (U/L)		78 (46-238)
Albumin (g/dL)		4.3 (2.9-4.97)
Calcium (mg/dL)		9.34 (6.48-10.97)
Ki-67 (%)		25 (2-90)
NLR		2.49 (0.59-13.50)
SII		687.14 (81.05-2708.18)

Table 2. Differences of groups with clinicopathologic and laboratory parameters.

Variables		Group I n= 16 (100%)	Group II n= 99 (100%)	p value
Age (years)		57.06 ± 12.87	53.67 ± 12.81	0.328
Menopausal status	Premenopausal	6 (37.5%)	45 (45.5%)	0.552
	Postmenopausal	10 (62.5%)	54 (54.5%)	
Breast side	Right	9 (56.3%)	46 (46.5%)	**0.031**
	Left	5 (31.3%)	52 (52.5%)	
	Bilateral	2 (12.5%)	1 (1%)	
Tumor type	IDC	16 (100%)	91 (91.9%)	0.698
	ILC	0 (0%)	6 (6.1%)	
	Mixt type	0 (0%)	2 (2%)	
T-stage	I	3 (18.8%)	38 (38.4%)	**0.003**
	II	6 (37.5%)	52 (52.5%)	
	III	6 (37.5%)	5 (5.1%)	
	IV	1 (6.3%)	4 (4%)	
N-stage	N (0)	0 (0%)	37 (37.4%)	**0.003**
	N (+)	16 (100%)	62 (62.6%)	
ER	Positive	14 (87.5%)	72 (72.7%)	0.207
	Negative	2 (12.5%)	27 (27.3%)	
PR	Positive	10 (62.5%)	61 (61.6%)	0.946
	Negative	6 (37.5%)	38 (38.4%)	
HER2	Positive	5 (31.3%)	34 (34.3%)	0.808
	Negative	11 (68.8%)	65 (65.7%)	
Luminal types	Luminal A	3 (18.8%)	17 (17.2%)	0.913
	Luminal B HER2 negative	7 (43.8%)	33 (33.3%)	
	Luminal B HER2 positive	4 (25%)	26 (26.3%)	
	HER2 like	1 (6.3%)	8 (8.1%)	
	Triple-negative	1 (6.3%)	15 (15.2%)	
CA 15-3 (U/mL)		87.44 (28-1841)	16.5 (3.3-313.7)	**<0.001**
CEA (ng/mL)		2.21 (0.54-43.75)	1.58 (0.01-138)	0.083
eGFR (mL/sc/1.73m^2)		90 (25.31-90)	90 (41-90)	0.080
Glucose (mg/dL)		98.5 (78-227)	102 (71-280)	0.765
ALP (U/L)		85.5 (53-238)	78 (46-196)	0.414
Albumin (g/dL)		3.95 (2.9-4.5)	4.3 (3.4-4.97)	**0.001**
Calcium (mg/dL)		9.07 (7.6-10.97)	9.39 (6.48-10.49)	0.166
Ki-67 (%)		35 (2-65)	25 (2-90)	0.266
NLR		3.05 (0.72-7.39)	2.42 (0.59-13.5)	0.074
SII		1030.8 (111.9-2069.4)	661.99 (81.05-2708.2)	0.075

between the groups in terms of age, menopause status, tumor type, hormone receptor status, luminal types, CEA, ALP, calcium, Ki-67, NLR, and SII levels (p> 0.05) (Table 2).

Univariate and multivariate analyses of metastasis prediction

The variables were evaluated using univariate analysis. T-stage, CA 15-3, eGFR, ALP, and albumin levels were statistically found to be significant. All these values were included in the multivariate regression analysis, and CA 15-3 (OR: 1.017; 95% CI: 1.005–1.030, p = 0.006), eGFR (OR: 0.944; 95% CI: 0.894–0.996, p = 0.034), and albumin (OR: 0.087; 95% CI: 0.011–0.676, p = 0.020) were found to be predictive risk factors for metastatic breast cancer (Table 3).

Discussion

In this study, high CA 15-3, low eGFR and low albumin levels were found to be risk factors for metastatic breast cancer at the time of initial diagnosis. This is the first study to compare metastatic versus non-metastatic breast cancers at the time of diagnosis.

The common serum marker for breast cancer metastasis, MUC-1 mucin glycoprotein CA 15.3, is not recommended for diagnostic or prognostic use due to its low sensitivity [11]. Although CA 15-3 is used in breast cancer patients during follow-up, it is not recommended for screening, diagnosis or follow-up after primary treatment by ASCO and

Table 3. Univariate and multivariate logistic regression analyses of predictive factors associated with metastatic breast cancer (*: analysis not applicable).

Variables	Univariate analysis OR (95%CI)	p value	Multivariate analysis OR (95%CI)	p value
Age (years)	1.021 (0.980-1.064)	0.326		
Menopausal status	1.389 (0.469-4.117)	0.554		
Breast side				
Right vs left	0.491 (0.154-1.572)	0.058		
Right vs Bilateral	10.222 (0.885-125.094)			
Tumor type*				
IDC vs ILC		1		
IDC vs mixt type				
T-stage				
I vs II	1.462 (0.344-6.216)	**0.005**		
I vs III	15.200 (2.860-80.774)			
I vs IV	3.167 (0.263-38.066)			
N-stage*		0.998		
ER	2.625 (0.559-12.321)	0.221		
PR	1.038 (0.349-3.089)	0.946		
HER2	0.869 (0.279-2.705)	0.808		
Luminal types				
Type A vs B Her2 negative	1.202 (0.275-5.247)			
Type A vs B Her2 positive	0.872 (0.173-4.392)	0.874		
Type A vs Her2 like	0.708 (0.063-7.919)			
Type A vs Triple-negative	0.978 (0.035-4.030)			
CA 15-3 (U/mL)	1.016 (1.003-1.029)	**0.012**	1.017 (1.005-1.030)	**0.006**
CEA (ng/mL)	1.013 (0.986-1.040)	0.359		
eGFR (mL/sc/1.73m^2)	0.963 (0.927-1)	**0.048**	0.944 (0.894-0.996)	**0.034**
Glucose (mg/dL)	1.003 (0.994-1.013)	0.493		
ALP (U/L)	1.016 (1.002-1.030)	**0.026**		
Albumin (g/dL)	0.064 (0.015-0.284)	**< 0.001**	0.087 (0.011-0.676)	**0.020**
Calcium (mg/dL)	0.605 (0.281-1.302)	0.199		
Ki-67 (%)	1.008 (0.983-1.033)	0.537		
NLR	1.155 (0.909-1.468)	0.238		
SII	1.001 (1-1.002)	0.052		

NCCN guidelines [5, 12]. Recent studies demonstrated a correlation between CA 15-5 levels and breast cancer's overall or disease-free survival [13-15]. According to previous researches, CA 15-3 levels are correlated with axillary lymph node status and distant metastasis [16, 17]. CA 15-3 levels were higher in distant metastatic breast cancer patients than non-metastatic patients at the time of initial diagnosis, prior to receiving any form of treatment [13]. CA 15-3 levels were found to be elevated in both primary and secondary metastatic breast cancer patients. We couldn't find a study in the literature that examined CA15-3 values only in metastatic breast cancers at initial diagnosis. This is the first study to compare CA 15-3 levels in metastatic versus non-metastatic breast cancer patients.

The association between cancer and eGFR has been demonstrated previously [18, 19]. While their relationship has not yet been explained in detail, tumor antigens have been implicated [20, 21]. The relationship between metastasis and eGFR has not yet been investigated in the literature. Therefore, we are unable to compare our results. In our study, the eGFR level was found to be lower in patients with metastatic breast cancer compared to non-metastatic patients. This could be due to an increase in tumor antigens caused by metastatic disease.

Albumin is a serum protein that may be used as an indicator of nutrition. Cachexia may occur in cancer patients due to increased energy consumption [22, 23]. As a result, a decrease in albumin level is possible. In studies, hypoalbuminemia was observed in cancer patients [22, 23]. Due to the increased number of metabolic foci associated with metastatic disease, it is possible that energy consumption will increase even further. In our study, patients with metastatic disease had even lower albumin levels. In addition, albumin was found to have a predictive value for metastatic disease.

In our study, metastatic disease was more common in the right breast. However, this situation was not observed as a predictive value. We think that this is caused by the limited number of patients. In the literature, there is no study that discriminates between sides.

Breast cancer survival and treatment depend on TNM staging. Patients with a higher T-stage are more likely to develop metastases to distant organs [24]. Along with distant organ metastasis, axillary lymph node metastasis also occurs [24]. Our findings were consistent with the literature.

The limited number of patients was the most significant limitation of our study. One important reason for this was the early diagnosis of patients by means of mammography scans. In addition, the study was retrospective, and there was no standard for metastasis detection.

Conclusion

In conclusion, Ca 15-3, eGFR, and albumin levels were found to be predictive risk factors for metastatic breast cancer at the time of diagnosis in this study. These results need to be supported by larger-scale studies. This is the first study to examine predictive risk factors in metastatic breast cancer patients at the time of diagnosis.

Ethical approval

The study was approved by the Noninvasive Research Ethics Committee of Fırat University (approval no. 2023/10-24).

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